REMARKS

Rejection Under 35 U.S.C. §103

Claims 11-16, 20-22, 30, 33-36, 40-42 are rejected as being obvious in view of the Goulding et al. article (1992). This rejection is respectfully traversed.

Goulding et al. discloses the results of a study in rats to determine whether Tamoxifen citrate could prevent the osteopenic effect (i.e., estrogen-deficiency bone loss) associated with the luteinizing hormone releasing hormone (LHRH) agonist buserelein. As set forth in the summary, Goulding et al. discloses that Tamoxifen citrate "is an estrogen agonist/antagonist which protects the skeleton from osteopenia when ovarian hormones are depleted."

In the study, four groups of rats were studied for four weeks. These groups were treated with a placebo, buserelein alone, Tamoxifen alone, or a combination or buserelein and Tamoxifen. The results show that the buserelein lowered 17 β-estrodiol values, both in the presence of Tamoxifen and in the absence of Tamoxifen. In addition, Tamoxifen was found to slow bone breakdown and inhibit the bone-thinning effects of buserelein. Total body calcium values were highest in the group that was treated with both buserelein and Tamoxifen. Osteopenia was exhibited only in the group to which buserelein was administered alone. In light of these results, Goulding et al. suggests that "the use of Tamoxifen to protect the skeleton during LHRH-agonist therapy in young women should be explored."

Goulding et al. makes no disclosure or suggestion with respect to using other estrogen agonist/antagonists in place of Tamoxifen. In fact, even in the case of Tamoxifen, Goulding et al. merely suggests that its use during LHRH-therapy "should be explored."

In the rejection, it is argued that it would be obvious to substitute other anti-estrogens in place of Tamoxifen. However, there is no suggestion of such a substitution by Goulding et al. Moreover, the rejection does not provide any suggestion that other anti-estrogens or estrogen agonist/antagonists such as Raloxifene will function in a manner similar to Tamoxifen.

Tamoxifen is (Z)-2-[4-(1,2-diphenyl-1-butenyl)-phenoxy]-N,N-dimethyl. The structure of Tamoxifen is shown in the attached excerpt from the *USP Dictionary of USAN in International Drug Names*. See page 685. As can be seen, this structure exhibits two carbon atoms attached to one another by a double bond which are then substituted by three phenyl

structures and one ethyl structure. There are no fused ring structures and no heterocyclic ring structures.

On the other hand, Raloxifene is 6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1piperidinyl)ethoxy]phenyl]-methanone. See page 615 of the attached excerpt from *USP Dictionary of USAN and International Drug Names*. The structure of this compound is significantly different than that of Tamoxifen. It has not only a fused ring structure but also two heterocyclic structures. There is nothing within the rejection that suggests that one of ordinary skill in the art would expect Raloxifen would act in a similar manner to Tamoxifen, particularly when used in conjunction with an LHRH agonist. Moreover, Raloxifene differs from Tamoxifen in that it lacks the adverse uterus stimulating activity associated with the latter. Thus, the rejection fails to present sufficient rationale to support the conclusion that one of ordinary skill in the art would find the substitution of Raloxifene for Tamoxifen to be obvious in light of the disclosure of the Goulding et al.

Furthermore, it is noted that Raloxifene and Tamoxifen are estrogen agonist/antagonists. Nothing in the rejection suggests that Raloxifene would act anti-estrogenic, rather than estrogenic, when used in combination with an LHRH agonist, especially in light of its significantly different structure in comparison to Tamoxifen.

Enclosed herewith is an excerpt from the prosecution history of Bryant et al. (U.S. 6,096,764). During prosecution of U.S. '764, the Examiner rejected claims as being obvious in view of an article by Draper (CA124:155994). In the Response filed April 27, 1999, the applicant argued that:

> One of the main questions to be answered, prior to the filing of the present application, was whether or not the compounds of formula I would still be able to inhibit bone loss and/or lower serum cholesterol when concurrently administered with GnRH (or a GnRH agonist). The outcome where GnRH interferes with the action of a compound of formula I, thus negating its protective effects, was at least as likely as the answer Applicants have provided herewith.

Following a final rejection, these arguments were essentially repeated in a Response filed October 19, 1999. A Notice of Allowability subsequently issued.

In view of the above remarks, it is respectfully submitted that Goulding et al. fails to render obvious applicants' claimed invention. Withdrawal of the rejection under 35 U.S.C. §103 is respectfully requested.

As a final note, at page 5 of the Office Action, Bryant et al. (U.S. 6,096,764) is inadvertently characterized as "prior art." U.S. '764 is not prior art with respect to the instant application which has an international filing date, and thus an effective U.S. filing date, of January 29, 1997, which is prior to the alleged priority date of August 21, 1997, for U.S. '764.

Respectfully submitted,

Brion P. Heaney (Reg. No. 32,542)
Attorney for Applicants

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
Arlington Courthouse Plaza I
2200 Clarendon Boulevard, Suite 1400
Arlington, Virginia 22201
Direct Dial: (703) 812-5308
Facsimile: (703) 243-6410
Internet Address: heaney@mwzb.com

Filed: October 30, 2001

BPH:imm\K:\Sch\1655\Reply 10-30-01.wpd

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Please delete claims 15, 16, 21, 22 and 41.

Please amend the 30, 34, 35, 36, and 42-44 as follows:

--**30.** A method according to claim 34, wherein said LHRH analogue is administered in the amount of 2 μg-20 mg per kilogram of body weight and Raloxifen ~~said anti-estrogen~~ is administered in an amount of 0.1 μg-10 mg per kilogram of body weight.

34. A method for ameliorating LHRH analogue-induced reduction in bone density in a patient comprising administering to said patient one or more LHRH analogues and Raloxifen ~~at least one anti-estrogen~~ wherein said one or more LHRH analogues and Raloxifen ~~said at least one anti-estrogen~~ are administered sequentially or simultaneously.

35. A method according to claim 34, wherein said LHRH analogue is Leuprorelin, Cetrorelix, Buserelin, Antide, Ac-D-Nal-D-Cpa-D-Pal-Ser-Tyr-D-Cit-Leu-Lys(Mor)-Pro-D-Ala-NH_2, Ramorelix, Zoladex or combinations thereof ~~and said anti-estrogen is Raloxifen, Droloxifen, Centchroman or combinations thereof~~.

36. A method according to claim 34, wherein Raloxifen ~~said anti-estrogen~~ is administered after administration of said LHRH analogue.

42. A method according to claim 41, wherein said LHRH analogue is Antide ~~and said anti-estrogen is Raloxifen~~.

43. A method according to claim 41, wherein said LHRH analogue is Ac-D-Nal-D-Cpa-D-Pal-Ser-Tyr-D-Cit-Leu-Lys(Mor)-Pro-D-Ala-NH_2 ~~and said anti-estrogen is Droloxifen~~.

44. A method of inhibiting LHRH analog-induced detrimental side effects due to the administration of an LHRH analog to a patient, wherein said detrimental side effect is reduction in bone density, comprising administering to a patient in need thereof an effective amount of ~~anti-estrogen wherein said anti-estrogen is~~ Raloxifen.- -

Please add the following new claims :

--51. A method for ameliorating LHRH analogue-induced reduction in bone density in a patient comprising administering to said patient one or more LHRH analogues and Raloxifen or a derivative thereof wherein said one or more LHRH analogues and Raloxifen, or a derivative thereof, are administered sequentially or simultaneously.

52. A method of inhibiting LHRH analog-induced detrimental side effects due to the administration of an LHRH analog to a patient, wherein said detrimental side effect is reduction in bone density, comprising administering to a patient in need thereof an effective amount of Raloxifen or a derivative thereof.--